40. (Twice Amended) An antivenom composition comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier[, wherein said venom comprises more than one toxin].

45. (Twice Amended) Fab fragments which bind specifically to a venom of a snake of the Crotalus genus, and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using an anti-Fc antibody[, wherein said venom comprises more than one toxin].

REMARKS

Applicants have cancelled claims 43-44 and 48-49 without prejudice or disclaimer, and Applicants have amended claims 40 and 45 to more distinctly recite the claimed invention. Upon entry of this amendment, claims 40-42 and 45-47 will be pending in this application.

This Amendment is supported by the First Declaration of Findlay E. Russell, M.D., Ph.D. ("the First Russell Declaration") and the Second Declaration of Findlay E. Russell, M.D., Ph.D. ("the Second Russell Declaration"), which Applicants file herewith. Applicants are filing unexecuted Declarations. They will file executed Declarations after they receive them from Dr. Russell.

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Rejection of Claims 40-45 Under 35 U.S.C. § 112, First Paragraph (Item 17)

The Examiner rejected claims 40-45 under 35 U.S.C. § 112, first paragraph, as allegedly not being supported by an adequate written description. Specifically, the Examiner contends that the specification does not support the recitation of "antivenom" in claim 40.

Applicants respectfully traverse this rejection. As Dr. Russell states in his First Declaration, the terms "antivenom" and "antivenin" are often interchanged. (First Russell Declaration at ¶ 17). Although Applicants used the term "antivenin" in the specification, the World Health Organization ("WHO") has decided that "antivenom" is preferred. (Id.) Applicants now use this term in the claims in compliance with the WHO's decision. Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejection of Claims 40-49 Under 35 U.S.C. § 112, First Paragraph (Item 18)

The Examiner rejected claims 40-49 under 35 U.S.C. § 112, first paragraph as allegedly not being supported by an adequate written description. Specifically, the Examiner contends that the specification, including the originally filed claims, does not support the recitation of "essentially free from contaminating Fc".

Applicants respectfully traverse this rejection. As the Examiner notes, original claims 27 and 29 recite no precipitation band; they do not recite essentially no

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precipitation band. Similarly, the specification states that Fig. 2 (the 48-hour digest) shows no precipitation band against anti-Fc antibodies. (Specification at 16-17).

However, for the four-hour digest, the specification states that Fig. 4 contains "a **slight hint** of a F(c) reaction." (Id. at 17, lines 27-28; emphasis added). Accordingly, one of ordinary skill in the art would have recognized that Applicants had possession of an antivenin comprising Fab fragments that are **essentially** free from contaminating Fc. Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejection of Claims 40-49 Under 35 U.S.C. § 112, First Paragraph (Item 19)

The Examiner rejected claims 40-49 under 35 U.S.C. § 112, first paragraph, as allegedly not being supported by an adequate written description. Specifically, the Examiner contends that the specification does not support the recitation that "said venom comprises more than one toxin" in claims 40 and 45.

Applicants respectfully traverse this rejection. Findlay E. Russell, M.D., Ph.D., was asked to comment upon this rejection. Dr. Russell stated that venoms are often very complicated mixtures of individual toxins and the Crotalidae snake venoms are particularly complicated. (Russell Declaration at ¶¶ 14-15). Those skilled in the art refer to each of these individual components of a snake venom as a "toxin." (Id. at ¶ 16).

Since those skilled in the art refer to each of the individual components of a snake venom as a "toxin," Dr. Russell explains that:

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> it would have been clear to a researcher in the field that we used the term "venom" in the subject patent application to mean a venom comprising several different toxins, not just a single toxin. Each venom discussed in the application contains several toxins. Furthermore, the application specifically discusses isolating specific venom proteins ("toxins") from the snake venom. Specification at 6, last sentence. Accordingly, a researcher in the field would have understood from the subject patent application that we used the term "venom" in the subject patent application to mean a mixture of toxins, not a single toxin isolated from a venom.

(Id. at ¶ 16).

In other words, the property of comprising more than one toxin is inherent in the term "venom." Accordingly, Applicants have deleted the express recitation of this property in claims 40 and 45 solely to expedite allowance of the pending claims, and not in acquiescence to this rejection. Since this rejection is moot, Applicants respectfully request its withdrawal.

Rejection of claims 41, 43, 46, and 48 Under 35 U.S.C. § 112, First Paragraph (Item 20)

The Examiner rejected claims 41, 43, 46, and 48 under 35 U.S.C. § 112, first paragraph, as allegedly not being supported by an adequate written description. Specifically, the Examiner contends that the specification does not support recitation of "IgG(T)" because the specification allegedly does not disclose the derivation of Fab from monoclonal IgG(T).

Applicants respectfully reverse this rejection. As the specification discloses, antivenoms are typically produced from horse serum. (Specification at 4, lines 19-22). Since horse serum contains large amounts of IgG(T), one skilled in the art would have

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understood that the specification's discussion of monoclonal antibodies as a source for the Fab fragments encompassed monoclonal IgG(T). Indeed, immediately after discussing deriving the antibody fragments of the claimed invention from monoclonal sources, the specification provides an example of deriving antibody fragments from IgG(T). (Specification at 5-6).

Even more clearly, Figure 8 illustrates the production of Fab fragments from IgG(T) and states that the "process can be used to isolate monoclonal antibodies and **monoclonal fragments**." (Emphasis added). Accordingly, one skilled in the art would have recognized that applicants had possession of the claimed invention, including the derivation of Fab fragments from monoclonal IgG(T), and applicants respectfully request withdrawal of this rejection.

The § 103 Rejections (Items 22 and 24)

The Examiner rejected claims 40-49 under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al., as evidenced by Stedman's Medical Dictionary. The Examiner also rejected claims 45-49 under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan et al. in view of Coulter et al. Applicants respectfully traverse both of these rejections, and Applicants treat these rejections together because they both fail for the lack of an expectation of success.

Dr. Russell was asked to comment on these rejections. Dr. Russell stated that the only commercially available antivenom in 1984 for North American Crotalidae

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snakes was Antivenin [Crotalidae] Polyvalent (equine origin) ("ACP"; Wyeth Laboratories, Philadelphia, PA), which first became available in 1947. This antivenom suffers the serious problem suffered by other antivenoms of often causing serum sickness, an allergic reaction to the antivenom that is sometimes as deleterious as the venom. Over 75% of ACP patients suffer from serum sickness. This danger can be so great that physicians may not administer this antivenom for some cases of envenomation, and ACP can only be obtained in a kit that also contains test serum for possibly detecting serum sickness. (First Russell Declaration at ¶ 20).

Because of the serious problem of serum sickness, extensive research had been performed on developing better antivenoms, much of this research focused on immunoglobulin fragments, which may not provoke an immune reaction. In the late 1960's, researchers began experimenting with antivenoms comprising $F(ab)_2$ fragments, and such antivenoms first became commercial available in 1969. Although the smaller size of the $F(ab)_2$ fragments results in less serum sickness, such antivenoms appear less effective than antivenoms comprising whole immunoglobulin. Consequently, Crotalidae antivenoms comprising $F(ab)_2$ fragments were not produced in the United States. (Id. at ¶ 24).

Although serum sickness has long been recognized as a major problem with antivenoms, and although smaller antibody fragments have long been known to be less immunogenic, no researcher developed antivenoms comprising the smaller Fab fragments prior to Applicants' invention. According to Dr. Russell, development of antivenoms comprising antibody fragments halted at the larger $F(ab)_2$ fragments

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because those of ordinary skill in the art expected that the smaller Fab fragments would be less effective than $F(ab)_2$ fragments. Indeed, they expected that Fab fragments would actually increase the lethality of Crotalidae venoms. (Id. at ¶ 25).

According to Dr. Russell:

> Researchers in the field were concerned that antivenoms comprising Fab fragments would be less effective than antivenoms comprising $F(ab)_2$ fragments because: 1) the Fab fragments would not prevent the various venom toxins from binding to their site of action as well as the $F(ab)_2$ fragments; 2) the Fab fragments would not precipitate the various venom toxins; and 3) the Fab fragments would not neutralize sufficient venom toxin before being cleared due to their short half-life.

(Id. at ¶ 26).

Furthermore, for reasons Dr. Russell explains in great detail in his First Declaration, those of ordinary in the skill in the art actually expected that such an antivenom would increase the lethality of the snake venom by redistributing and concentrating the toxins, converting localized toxicities to systemic toxicities. (Id. at ¶¶ 32-41).

In sum, prior to Applicants' invention, those of ordinary skill in the art did not have a reasonable expectation of success that an antivenom comprising Fab fragments to Crotalidae venom would be effective. Despite the known problems with the commercially available venom for Crotalidae envenomation since 1947, and the well-known fact that smaller immunoglobulin fragments are less immunogenic, those of ordinary skill in the art had not progressed beyond antivenoms comprising the $F(ab)_2$ fragments to the smaller Fab fragments because they expected them to be ineffective.

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The Examiner has criticized the Smith and Sullivan Declarations as allegedly ignoring the Coulter *et al.* reference's alleged teaching that Fab antivenin can neutralize a toxin from snake venom. (Paper No. 29 at 5, first full paragraph). Although Applicants respectfully submit that their prior submissions, including the Smith and Sullivan Declarations, address the teachings of the Coulter *et al.* reference, Dr. Russell was asked to expressly address the Coulter *et al.* reference at length in his Declaration. Dr. Russell makes three points about the Coulter *et al.* reference, each of which shows that one of ordinary skill in the art would not have had a reasonable expectation of success regarding the claimed invention in light of the cited references.

First, Dr. Russell states that Coulter *et al.* used a single toxin from the Australian brown snake, *Pseudonaja textilis*. In contrast, the pending claims recite a snake of the genus *Crotalus*, a genus of the family Crotalidae. As its name ("Pseudonaja") indicates, the Coulter *et al.* snake is not a member of the genus *Crotalus*, nor even of the family Crotalidae. Indeed, it is of the family Elapidae. (First Russell Declaration at ¶ 45).

Second, Dr. Russell explains that textilotoxin is simply one isolated toxin from Australian brown snake venom. The terms "antivenin" and "antivenom" mean an immunotherapy mixture against a snake venom, which comprises many substances that act synergistically and can induce autopharmacologic reactions *in vivo*. Basic toxicology texts expressly caution against extrapolating results from individual venom toxins to whole venoms. Accordingly, one of ordinary skill in the art would not have expected Coulter *et al.*'s results with Fab to a single toxin to predict similar results with Fab to Crotalidae snake venom. (Id. at ¶ 46).

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Finally, and most importantly, Dr. Russell explains that Coulter *et al.* did not treat envenomation with Fab fragments. Rather, Coulter *et al.* mixed Fab fragments with textilotoxin *in vitro* and then injected the Fab-textilotoxin mixture intravenously. Coulter *et al.*'s neutralization results would not have provided an expectation of success for the claimed invention because their *in vitro* mixing and intravenous injection avoided the processes that led those of ordinary skill in the art to expect that a Crotalidae antivenom comprising Fab fragments would increase the lethality of the snake's venom. (Id. at ¶ 47). Accordingly, the Russell Declaration has not ignored any teachings of the Coulter *et al.* reference, and it has shown that one of ordinary skill in the art would not have had a reasonable expectation of success.

Finally, although the Examiner did not expressly cite Sullivan (1986) in his statement of the rejection, the Examiner later relied on several teachings from this reference. (Paper No. 29 at 5, first three paragraphs). Applicants previously noted that Sullivan (**1986**) is not available as prior art because the present application is entitled to a filing date of October 9, **1984**. Indeed, Sullivan (1986) reports work contained in the present application. In the interest of compact prosecution, Applicants respectfully request that the Examiner acknowledge that Sullivan (1986) is not available as prior art or that the Examiner provide some justification for relying upon the teachings in this article.

For the above reasons, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103.

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Rej ction of Claims 43-44 and 48-49 Under U.S.C. § 112, Second Paragraph (Item 23)

The Examiner rejected claims 43-44 and 48-49 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner contends that claim 43 is substantially duplicative of claim 41 because both claims read on the same product and that claim 44 is substantially duplicative of claim 42 for the same reason.[1] Applicants have cancelled claims 43-44 and 48-49 without prejudice or disclaimer. Accordingly, this rejection is moot, and Applicants respectfully request its withdrawal.

Rejection of Claims 40-49 Under 35 U.S.C. § 102(a) (Item 26)

The Examiner rejected claims 40-49 under 35 U.S.C. § 102(a) as allegedly being anticipated by Sullivan et al. (Veterinary and Human Toxicology). Applicants respectfully traverse this rejection.

Applicants file herewith the Second Declaration of Findlay E. Russell, M.D., Ph.D. Under 37 C.F.R. § 1.132. This Declaration states that the Applicants are the true inventors of the subject matter disclosed and claimed in both the present application and the subject matter disclosed in the Sullivan *et al.* abstract. Furthermore, the Declaration demonstrates that co-authors Ned Egan and Michael Owens did not make an inventive contribution to the subject matter presently claimed in this application. Accordingly, the Sullivan *et al.* abstract is not available as prior art against this

[1] Applicants note that the Examiner has not rejected claims 46 and 47 on this ground, but the Examiner does discuss these claims in the rejection.

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application, In re Katz, 215 U.S.P.Q. 14 (C.C.P.A. 1982), and Applicants respectfully request withdrawal of this rejection.

If any other fees are due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested, and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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By: _____
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